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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/375,924	08/17/99	GALLO M	ABGX-2-CIP

EXAMINER	
DIBRINO, M	
ART UNIT	**PAPER NUMBER**
1644	17

HM22/0705

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DATE MAILED: 07/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/375,924	Gallo et al
Examiner	**Art Unit**
Marianne DiBrino	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Aug 22, 2000, 5/19/00, 11/20/00, 1/19/01 & 4/23/01

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 12-43 is/are pending in the applica

4a) Of the above, claim(s) 27-43 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 12-26 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) ~~Paper No(s).~~ filed 5/19/00

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☒ Other: *Notice to Comply with the Sequence Rules*

DETAILED ACTION

1. Applicant's amendment filed 8/22/00 and Applicant's responses filed 5/19/00, 11/20/00, 1/19/01 and 4/23/01 are acknowledged and have been entered.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice to comply with the sequence rules.

It is noted that Applicant's response filed 4/23/01 has checked a submission of a substitute CRF; however, the Biotechnology Systems Branch of the Scientific and Technical Information Center (STIC) is not in receipt of the said CRF.

3. Claims 12-43 are pending and are presently being examined.

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the declaration is required to cite priority to the provisional application under 35 U.S.C. 119(e).

Regarding Applicant's comments in the amendment filed 8/22/00 on page 9 under "Oath or Declaration", Applicant has claimed priority under 35 U.S.C. 119 in the declaration, but not under 35 U.S.C. 119**(e)**.

The following are new grounds of rejection necessitated by Applicant's amendment filed 8/22/00.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Applicant is reminded of the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999. The following rejection is set forth herein.

Claims 12-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method of extending the serum half life of a protein having a first region capable of binding to an FcRb receptor, the method comprising joining to said protein at least a second region capable of binding to an FcRb receptor.

The instant claims encompass a protein and methods thereof, wherein the said protein comprises a first region and/or second regions can be any moiety that is capable of binding to an FcRb receptor and which is not an IgG Fc region or an IgG antibody. In addition, claims 42 and 43 encompass a protein and method thereof, which binds to any receptor, and wherein the first and second regions that bind to the said receptor can be any regions that bind to any receptor. There is insufficient disclosure in the specification on such a protein and method comprising/use of the said first or second regions.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

The instant specification on page 25 at lines 13-25 discloses that "where the first FcRn binding moiety is an IgG antibody that ordinarily binds to FcRn and the second FcRn binding moiety is a molecule containing the CH2 and CH3 domains from an IgG Fc that ordinarily binds FcRn, the molecule expressed may essentially been considered as an IgG antibody possessing a CH2 and CH3 domain dimer in its Fc region", and Figure 1A discloses an Fc Region of an antibody (conjugated to an IgG Fc region shown in Figure 1B). The specification on page 26 at lines 6-11 discloses that compositions of the invention can be said to comprise at least two regions that bind to an FcRn, and the regions may be the same or different. The specification further discloses on page 26 at lines 26-36 that the FcRn binding moiety need not be restricted to native forms of the FcRn binding moieities that are present in the Fc of IgG, but rather can be generated through mutagenesis studies of Fc from IgG followed by screening for binding with FcRn, or peptide or polypeptide libraries can be screened for such binding. The specification also discloses that cell surface receptors including channel linked, g-protein linked and

catalytic receptors all interact with specific ligands, and would be amenable to a strategy of adding additional binding domains for enhancement of avidity (especially page 29 at lines 6-15). The specification also discloses other systems amenable to the said strategy include cytokine receptors, receptors that inhibit adenylate cyclase, endocrine, paracrine and synaptic systems, steroid hormone, channel proteins, or any system that involves protein interactions (pages 29 and 30).

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as "a first region" and "at least a second region" "capable of binding to an FcRb receptor" is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being capable of binding to an FcRb receptor. It does not specifically define any of the "regions" that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by the property of being "capable of binding to an FcRb" does not suffice to define the genus because it is only an indication of what some general property the "region" has. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.").

The instant disclosure of IgG antibodies comprising Fc regions or of IgG Fc regions is insufficient to does not adequately describe the scope of the claimed invention, which encompasses a substantial variety of subgenera. Since the disclosure fails to provide sufficient relevant identifying characteristics that identify members of the genus, and given the broad genus claimed, the disclosure of IgG antibodies comprising Fc regions or IgG Fc regions is insufficient to describe the claimed genus.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 12-43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 12, 17, 18, 25-27, 32, 33 and 40-43 are indefinite in the recitation of "region" because it is not clear what this term encompasses.

b. Claims 12, 24, 39 and 42 are indefinite in the recitation of "joining" because it is not clear what this term encompasses.

c. Claims 25, 40 and 43 are indefinite in the recitation of "joined" because it is not clear what this term encompasses.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 12-19, 21, 22, 24-34, 36, 37, 39, 40, 42 and 43 are rejected under 35 U.S.C. 102(a) as being anticipated by Junghans (WO 97/43316) and the admission in Applicant's amendment filed 8/22/00 on page 11 at lines 27 and 28 and the footnote on page 12.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater , 162 USPQ 541, 550 - 51 (CCPA 1969).

Junghans teaches that the FcRp and the FcRn are the same receptor (especially page 2, lines 16-21). Junghans teaches a method for producing an antibody which has an extended half-life in the circulatory system of a subject comprising modifying the structure of an antibody by recombinant means which has a first FcRn binding domain (especially claims 19, 23, 26, 27 and Table 1). "VLHQ" (especially first four amino acid residues of SEQ ID NO: 9, 5th line of Table 1 in column 3) and "HNHY" (especially last line of column 3 in Table 1) are two exogenous FcRn binding domains (especially lines 30-36 on page 7 and line 1 on page 8). Junghans teaches a modified antibody which has an extended half-life in a subject (including mammals) comprising at least a first and second FcRn binding domain physically linked to a constant region of the antibody (especially claims 1, 5, 6, 10 and Table 1). Junghans also teaches an IgA molecule (IgA is a dimer) which is altered recombinantly to possess three FcRn binding domains "KTLMISRTP" (the second line of column 3 in Table II, SEQ ID NO: 12 exclusive of amino acid residue number 1), "VLHQ" (the fifth line of column 3 in Table II, amino acid residues 1-4 of SEQ ID NO: 9) and "HNHY" (the last line of column 3 in Table II, SEQ ID NO: 9). Junghans further teaches an antibody or antigen-binding fragment of an

antibody produced against the FcRp which is included as a modification to another molecule (especially page 3, lines 23-25). Junghans teaches that this other molecule can be an immunoglobulin (especially page 4, lines 7-13). The claimed molecule appears to be the same as the art absent a showing of any differences. Since the Patent Office does not have the facilities for examining and comparing the molecule of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the molecule of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). (especially page 19 at lines 1-4), i.e., Junghans teaches "joining". Junghans teaches IgG molecules (especially page 5 at lines 19-21) that can be joined, including as a fusion protein, to carrier molecules comprising FcRp binding "carriers" (especially page 11 at lines 25-36 and page 12 at lines 1-3). Junghans teaches compositions comprising the said molecules and proteins (especially page 12 at lines 4-6). The admission in Applicant's amendment filed 8/22/00 on page 11 at lines 27 and 28 and the footnote on page 12 is that Applicant acknowledges the equivalence of the FcRp, FcRn and FcRb receptors.

With regard to the limitation of the instant claims of a region "capable of binding to an FcRb receptor" and the sequences taught by Junghans, the "region" recited in the claimed method appears to be the same as the art absent a showing of any differences. Since the Patent Office does not have the facilities for examining and comparing the molecule of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the molecule of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

The reference teachings anticipate the claimed invention.

Applicant's arguments in the amendment filed 8/22/00 have been fully considered but are not persuasive.

It is Applicant's position in the said amendment on page 12 beginning at line 24 that Junghans et al does not teach "joining".

It is the Examiner's position that the limitation "joining" is broad, and that the said limitation therefore encompasses the teaching of Junghans et al of insertion of the Brambell motif into a protein as well as the modification of nucleic acid codons encoding amino acid residues that pre-exist in a protein to encode a Brambell motif sequence.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 12-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Junghans (WO 97/43316) in view of Doerschuk et al (U.S. Patent No. 5,702,946), Junghans (Immunologic Research, 1997, Vol. 16, pages 29-57) and Braxton (U.S. Patent No. 5,766,897).

Junghans teaches that the FcRp and the FcRn are the same receptor (especially page 2, lines 16-21). Junghans teaches a method for producing an antibody which has an extended half-life in the circulatory system of a subject comprising modifying the structure of an antibody by recombinant means which has a first FcRn binding domain (especially claims 19, 23, 26, 27 and Table 1). "VLHQ" (especially first four amino acid residues of SEQ ID NO: 9, 5th line of Table 1 in column 3) and "HNHY" (especially last line of column 3 in Table 1) are two exogenous FcRn binding domains (especially lines 30-36 on page 7 and line 1 on page 8). Junghans teaches a modified antibody which has an extended half-life in a subject (including mammals) comprising at least a first and second FcRn binding domain physically linked to a constant region of the antibody (especially claims 1, 5, 6, 10 and Table 1). Junghans also teaches an IgA molecule (IgA is a dimer) which is altered recombinantly to possess three FcRn binding domains "KTLMISRTP" (the second line of column 3 in Table II, SEQ ID NO: 12 exclusive of amino acid residue number 1), "VLHQ" (the fifth line of column 3 in Table II, amino acid residues 1-4 of SEQ ID NO: 9) and "HNHY" (the last line of column 3 in Table II, SEQ ID NO: 9). Junghans further teaches an antibody or antigen-binding fragment of an antibody produced against the FcRp which is included as a modification to another molecule (especially page 3, lines 23-25). Junghans teaches that this other molecule can be an immunoglobulin (especially page 4, lines 7-13). Junghans also teaches insertion of the Brambell motif into a protein (especially page 19 at lines 1-4), i.e., Junghans et al teach "joining". Junghans teaches IgG molecules (especially page 5 at lines 19-21) that can be joined, including as a fusion protein, to carrier molecules comprising FcRp binding "carriers" (especially page 11 at lines 25-36 and page 12 at lines 1-3). Junghans teaches compositions comprising the said molecules and proteins (especially page 12 at lines 4-6).

Junghans does not teach said antibody binds specifically to IL-8, nor that the antibody is human.

The admission in Applicant's amendment filed 8/22/00 on page 11 at lines 27 and 28 and the footnote on page 12 is that Applicant acknowledges the equivalence of the FcRp, FcRn and FcRb receptors.

Doerschuk et al discloses anti-IL-8 monoclonal antibodies and their use in treatment of inflammatory disorders (especially Abstract). Doerschuk et al further teach methods of production of human monoclonal antibodies with anti-IL-8 specificity (especially column 11 at lines 4-17 and column 12 at lines 13-19)

Junghans (Imm. Res.) teaches that at low serum IgG concentrations the FcRn receptor binds all endocytosed IgG and efficiently returns the IgG to circulation, yielding a long IgG survival, but at high IgG concentrations, the receptor is saturated by IgG and the major fraction of the IgG is unbound by the receptor and passes to catabolism, yielding a more rapid net catabolism and abbreviated survival (especially page 34, last paragraph of column 1 and continuing on to column 2).

Braxton discloses the development of protein therapies is hampered by the relatively short half-life of proteins after administration (especially column 1, lines 47-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a human antibody with the anti-IL-8 specificity of Doerschuk et al as the modified antibody in the invention of Junghans et al (WO 97/43316) given the teaching of Junghans (Imm. Res.) of the saturation of FcRn at high serum IgG concentrations and the disclosure of Braxton of the need for increasing the short half-life of therapeutic proteins after administration for use as a therapeutic agent in humans as disclosed by Doerschuk.

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the human anti-IL-8 antibody of Doerschuk et al to comprise at least a first and second FcRn binding domain in order to increase the half-life in circulation as taught by Junghans et al for therapeutic use in inflammatory disorders as taught by Doerschuk et al, especially given the teaching of Junghans et al of a direct relationship between serum IgG concentration and its catabolic rate and the disclosure Braxton of the desirability of increasing the half life of therapeutically administered proteins. Claims 26 and 41 are included in this rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used identical FcRn binding regions that are effective.

Applicant's arguments in the amendment filed 8/22/00 have been fully considered but are not persuasive.

It is Applicant's position beginning on page 14 and continuing on to pages 15 and 16, that the sequences taught by Junghans are not FcRn binding domains. Applicant cites Zuckier et al. It is Applicant's further position that Junghans teaches modification rather than addition of amino acid sequences. It is also the Applicant's position that the modification of native antibodies taught by Junghans is limited to modification of those that bind poorly or not at all to FcRp, and that Junghans does not suggest that modification could usefully be the addition of at least a second region capable of binding FcRb to a molecule that has a first region capable of binding efficiently to an FcRb receptor such as an antibody of the IgG1, IgG2a or IgG2b subclass. The Applicant argues the remainder of the references individually.

It is the Examiner's position that Applicant has not provided evidence that individual sequences or combinations of sequences taught by Junghans are not sufficient to bind to FcRn, as the claims now recite regions capable of binding to an FcRb receptor. Applicant has not provided a copy of Zuckier et al. (See item #13 below of this Office Action). It is the Examiner's further position that the instant claims recite "joining" rather than "addition of amino acid sequences", and in addition, Junghans also teaches insertion of the Brambell motif into a protein, and so Junghans meets the claim limitation "joining". It is also the Examiner's position that the instant claims are not limited to an antibody of the IgG1, IgG2a or IgG2b subclass.

13. The information disclosure statement filed 5/19/00 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Marianne DiBrino

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
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June 19, 2001

Christina Chan

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640

Application No.: 09/375,924

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [X] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, **as indicated on the copy of the marked -up "Raw Sequence Listing" mailed 4/2/01.**
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other:

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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